REMARKS

1. STATUS OF THE CLAIMS

Claims 1-35 were originally filed in the application. Claims 4, 5, 8-17, 32, 34 and 35 were canceled and claims 18 and 27 were amended in an Amendment and Response mailed June 7, 2000. An identical Amendment and Response was mailed October 20, 2000; replacing the previous Amendment and Response. Claims 19, 25, and 33 were canceled and claims 1, 6, 7, 18, 20, 21, 26, and 27 were amended in an Amendment and Response mailed June 26, 2002. This Amendment and Response was resubmitted on October 10, 2002. Accordingly, claims 1-3, 6-7, 18, 20-24, and 26-31 are currently pending.

2. REJECTION OF CLAIMS 1-3 AND 6-7 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-3 and 6-7 are rejected under 35 U.S.C. § 112, First Paragraph, for allegedly not being enabled. The present rejection is respectfully traversed.

A. Predictability

The Examiner alleges that endotoxic shock is not predictable (see page 3, lines 8-9 of the Office Action). Endotoxic shock is not the claimed invention; therefore, the present allegation is moot and should be withdrawn. Furthermore, the specification discloses that the claimed method of conferring resistance to endotoxic shock is predictable (see, for instance, Example 4 at page 23, lines 9-23 of the specification).

B. Acceptance of the Claimed Invention

The Examiner alleges that one of ordinary skill in the art would not accept that administration of OB-R agonist ligand would be capable

of achieving the required result of conferring resistance to endotoxic shock within the necessary period of time.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. There is no statutory requirement that one of ordinary skill in the art accept the claims. The present rejection should be withdrawn.

C. Evidence to Support Allegation

The Examiner has not provided any evidence to support an allegation that the present claims are not enabled. The Examiner must provide evidence to rebut the assertions of enablement made in the specification (see, e.g., page 14, lines 26-29 of the specification).

The Applicant respectfully submits that the specification provides enabling disclosures in view of information in the art. The specification describes how to make an OB-R agonist ligand (see, e.g., Example 2 at page 20) and how to use the OB-R agonist ligand to confer resistance to endotoxic shock (see, e.g., Example 4, page 23, lines 9-23, with results displayed graphically in Figure 11).

Referring to Example 4 and Figure 11, two groups of mice are given an ordinarily 100% lethal dose (LD100) of LPS which is an art accepted model system for endotoxic shock in humans and lower animals. A therapeutically effective amount of OB-R agonist ligand is administered to one group of mice. The other group of mice, receiving LPS only, has a 100% mortality rate. The group of mice receiving LPS and OB-R has a 0% mortality rate over the course of the study.

These disclosures demonstrate that administering an OB-R agonist ligand to an animal confers resistance to endotoxic shock in the animal. These disclosures further demonstrate that the claimed invention is enabled. The Examiner has failed to provide evidence to

support an allegation of lack of enablement. Accordingly, the present rejection should be withdrawn.

D. Time Period Required

The Examiner alleges that there is a necessary time period required for the claimed method to confer resistance to endotoxic shock. The claimed invention is not limited by a necessary time period. Administration of an OB-R agonist ligand can be of benefit in conferring resistance to endotoxic shock at any time point. For example, in one embodiment an OB-R agonist ligand is administered after the LPS is administered. The LPS induces endotoxic shock, but the OB-R agonist ligand confers resistance to the endotoxic shock even when the OB-R agonist ligand is administered after the LPS. See, e.g., page 7, lines 3-5. The Applicant respectfully requests that the present basis for rejection be withdrawn.

E. Additional Factors of Consideration

The Applicant notes that there is a high level of skill in the art. One of ordinary skill in the art of the present invention typically has an advanced degree(s) and years of technical experience.

F. Guidance in the Specification

The Examiner alleges that the specification provides no guidance nor working examples as to how conferring resistance to endotoxic shock can be achieved. The Applicant respectfully directs the Examiner to the above arguments and to Example 4 which discloses a working example of the method of the present claims. The allegation that no guidance nor working examples are provided by the specification is without merit and should be withdrawn.

G. Undue Experimentation

The Examiner alleges that it would require undue experimentation to determine how to use the claimed invention because OB-R is a molecule which will down regulate upon activation, therefore, it is allegedly not clear how prior administration in anticipation of endotoxic shock would result in a system that is responsive enough to OB-R agonist ligand to result in resistance to endotoxic shock.

No evidence is offered by the Examiner to support the present allegation. Therefore, this allegation is conclusory, does not state the factual basis of the allegation, and this basis of rejection should be withdrawn.

The specification discloses that administering an OB-R agonist ligand, as claimed, does confer resistance to endotoxic shock. See the following, for instance.

> However, in the experimental group, OB protein treatment conferred mice complete resistance to this dose [10 microgram LPS per gram of body weight] of endotoxin. The OB-treated mice displayed noticeably less severe symptoms of endotoxemia, remaining alert and responsive to touch and other manipulation, and recovering quickly. See page 23, lines 19-23 and FIG. 11.

Of note, in the absence of the administration of OB, a dose of 10 microgram LPS per gram of body weight induces endotoxic shock and is a lethal dose in 100% of the animals (LD100). Thus, the specification discloses that administration of an OB-R agonist ligand confers resistance to endotoxic shock as claimed. While a working example is not required, the disclosure of a working example in the present specification demonstrates one skilled in the art can make and use the claimed invention in view of the disclosure and knowledge available in the art without undue experimentation.

The Applicant respectfully requests that the Examiner withdraw

the present rejection of claims 1-3 and 6-7 and place claims 1-3 and 6-7 in condition for allowance.

3. REJECTION OF CLAIMS 18, 20-24, and 27 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 18, 20-24, and 27 are rejected under 35 U.S.C. § 112, First Paragraph, for allegedly not being enabled. The present rejection is respectfully traversed.

A. All Agents Encompassed

The Examiner alleges that the claims encompass all agents which regulate expression of OB-R such as antisense, ribozymes, and other expression regulatory agents which are allegedly not predictive one from the other (see page 4, lines 7-9 of the Office Action).

However, claims 18, and 20-24 are directed to a method of treating a patient having obesity comprising a step of administering a "compound capable of inducing OB-R expression selected from the group consisting of LPS, IL-1α, IL-1β, TNF-α and IL-6; and administering a physiologically effective amount of an OB-R agonist ligand". Thus, the claims recite 1) inducing OB-R expression, not regulating expression of OB-R and 2) an explicit list of five compounds capable of inducing OB-R expression, not all agents such as antisense, ribozymes, and other expression regulatory agents. Each of the five compounds (LPS, IL-1α, IL-1β, TNF-α and IL-6) are asserted and demonstrated in the specification to induce OB-R expression (see e.g., page 4, lines 17-20 and Example 1 at page 16). The present allegation is misapplied.

Claim 27 is directed to a method for inducing OB-R expression in an animal, comprising "administering to the animal IL-6" and "administering to the animal recombinant OB protein". Again, the present allegation that "the claims encompass all agents which regulate expression of the OB-R" is misapplied.

The basis of the present rejection is an improper characterization of the claims; therefore, the rejection should be withdrawn.

B. Gene Expression Alleged to be Unpredictable

The Examiner alleges that the "regulation of gene expression is unpredictable" (see page 4, line 9 of the Office Action). The Examiner has improperly characterized the claims. The "regulation of gene expression" is a broad field that encompasses many diverse aspects of molecular biology. Claims 18, and 20-24, on the other hand, are directed to a method of treating a patient having obesity comprising a step of administering LPS, LPS, IL-1α, IL-1β, TNF-α or IL-6, capable of inducing OB-R expression; and administering an OB-R agonist ligand. LPS, LPS, IL-1α, IL-1β, TNF-α and IL-6 are disclosed to be capable of inducing OB-R expression. See, for instance, page 4, lines 17-20 and Example 1.

Claim 27 is directed to a method for inducing OB-R expression in an animal, comprising administering IL-6 and administering recombinant OB protein to the animal.

It is not necessary to enable the field of the "regulation of gene expression", only the claims as recited. The Applicants respectfully request that the present basis of rejection be withdrawn.

C. Antisense and Gene Therapy

The Examiner has improperly characterized the claims by alleging that the claims encompass the fields of "antisense" and "gene therapy" (see page 4, line 10 of the Office Action). Antisense and gene therapy include diverse aspects of molecular and cellular biology and medicine, while claims 18, and 20-24 are directed to the treatment of obesity comprising administering a compound selected from LPS, IL-1α, IL-1β, TNF-α and IL-6; and administering an OB-R agonist ligand.

Claim 27 is directed to inducing OB-R expression using IL-6 and OB protein. The elements of the present claims are enabled by the specification. It is not necessary to enable the fields of "antisense" and "gene therapy". The Applicants respectfully request that the present basis of rejection be withdrawn.

D. Wish to Know

The Examiner alleges on page 4, lines 14-17 of the Office Action that an assay to ascertain appropriate inducers is a "wish to know" those agents which could be used in the claimed method. The Examiner further alleges that the skilled artisan is required to "identify which agents may have potential in the claimed method" and that the skilled artisan is required to "develop the experimental protocol for the method to be functional".

Claims 18 and 20-24 are directed, in part, to a step of administering a compound capable of inducing OB-R expression selected from a group consisting of LPS, IL-1α, IL-1β, TNF-α and IL-6. Claim 27 is directed to a method of inducing OB-R expression using IL-6 and OB protein.

Thus, the inducers are expressly identified in the claims. Accordingly, no "assay" is required to "ascertain appropriate inducers", the skilled artisan is not required to "identify which agents may have potential in the claimed method", and the skilled artisan is not required to "develop the experimental protocol for the method to be functional".

The present allegations are based upon an improper characterization of the claims. The Applicants respectfully request that the basis of the present rejection be withdrawn.

E. Subject Matter of Claim 26 and Claim 27

Referring to claims 26 and 27, the Examiner alleges that claim 27

as indicated by the Applicant should be claim 26 (see page 5, line 1 of the Office Action). The Applicant notes that claim 26 was not rejected under 35 U.S.C. § 112.

The subject matter of the currently pending claim 26 was originally filed as claim 26 and amended to depend from claim 18, instead of claim 25, in a response filed June 26, 2002, wherein claim 25 was cancelled. The subject matter of claim 26 has remained essentially unchanged throughout the prosecution of the present application.

Claim 27 was originally filed in the patent application and amended by responses filed June 7, 2000 (a duplicate response was filed October 20, 2000) and June 26, 2002. The subject matter of claims 26 and 27 have not been interchanged during the prosecution of the present application. The Applicants request clarification regarding the statements at the top of page 5 concerning claims 26 and 27.

F. Enablement of Claim 27

The discussions at page 5, lines 1-16, as applied to claim 27, are not relevant, and will not be addressed since claim 27 does not recite "treatment of a patient" as stated at line 3 on page 5 of the Office Action.

The Examiner next argues non-enablement of claim 27 based on the allegation that OB administration results in binding of the OB-R and subsequence down regulation of the receptor (page 5, lines 18-19 of the Office Action). The present allegation is conclusory. The Examiner does not support the allegation with a factual basis or evidence demonstrating 1) that OB administration results in down regulation of the OB receptor as alleged or 2) how the alleged "subsequence down regulation of the [OB] receptor" is relevant to the method of claim 27.

The specification, on the other hand, does assert and demonstrate that administration of IL-6 induces OB-R expression. See, e.g., page 4, lines 17-20; page 16, lines 5-7; page 20, lines 17-18; and Example 1 of the specification. Regarding the administration of OB, the specification discloses, for example, that administering an OB agonist ligand in combination with an OB-R expression inducer [e.g., IL-6] is useful to counteract the possible toxic side effects of the OB-R expression inducer. See page 14, lines 3-13, for example.

The Examiner next alleges that there "is not a single example in the instant specification which co-administered IL-6 and OB and then determined that OB receptor was induced" (page 5, lines 19 and 20). Of note, a working example is not a statutory requirement of enablement. See, *Ex parte* Nardi and Simier, 229 USPQ 79, 80 (BOPA, 1986). Furthermore, claim 27 does not require the limitation that the IL-6 and OB protein be co-administered.

The Examiner next alleges that one of ordinary skill in the art would not expect that OB receptor expression was induced by co-administered IL-6 and OB and; therefore, the claims are allegedly not enabled (page 6, lines 1-2 of the Office Action). No support is offered by the Examiner to indicate why a skilled artisan would not expect the result, and therefore this argument is conclusory, without basis, and should be withdrawn.

Furthermore, as discussed above, the specification discloses a method of inducing OB-R expression comprising administering IL-6. See, e.g., page 4, lines 17-20; page 16, lines 5-7; page 20, lines 17-18; and Example 1 of the specification. The specification also teaches that administering an OB agonist ligand in combination with an OB-R expression inducer [e.g., IL-6] is useful to counteract the possible toxic side effects of the OB-R expression inducer. See page 14, lines 3-13, for example. The disclosures in the specification, in view of the knowledge in the art, would enable the skilled artisan to make and

use the claimed invention.

In view of the above arguments, the Applicant respectfully requests that the Examiner withdraw the present rejection of claim 27, and place claim 27 in condition for allowance.

4. REJECTION OF CLAIMS 18, 20-24, 26, and 28-31 UNDER 35 U.S.C. § 102/103

a. REJECTION UNDER 35 U.S.C. § 102

The rejection of claims 18, 20-24, 26, and 28-31 under 35 U.S.C. § 102 is not expressly repeated in the present Office Action and; therefore, has been overcome and withdrawn (see page 2, paragraph 3 of the Office Action).

b. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 18, 20-24, 26, and 28-31 are rejected under 35 U.S.C. § 103(a) as allegedly not being patentable over Grunfeld et al (J. Clin. Invest. 97(9):2152-2157, 1996). The present rejection is respectfully traversed.

The Examiner alleges that one of ordinary skill in the art at the time of the invention would readily ascertain that co-administration of OB and inflammatory endotoxins or cytokines would be useful for treating conditions requiring anorexia, or weight loss (page 6, lines 11-15 of the Office Action).

There is no evidence in the cited reference that the skilled artisan, confronted with same problems as inventor and with no knowledge of claimed invention, would select elements from cited prior art reference for combination in manner claimed. An implicit, generalized finding that person of ordinary skill in art, faced with same problem as inventor, would have found claimed combination obvious is insufficient to establish obviousness. See, e.g., *Ecolochem Inc. v.*

Southern California Edison Co., 227 F.3d 1361, 56 USPQ2d 1065(Fed. Cir. 2000).

The Examiner has made a generalized finding that the claimed combination is obvious. No evidence is provided that the cited reference suggested the claimed combination. Specific passages in Grunfeld are not identified which name the administration of the compounds recited in independent claims 18 or 28 because Grunfeld does not name such compounds for the claimed use. The Examiner has failed to support a prima facie case of obviousness

Next, the Examiner alleges (at page 6, lines 18-20) that one would be "motivated to use the claimed combination of agents because the administration of an agent which induces expression of OB would enhance the anorexic response and [allegedly] would increase the patient's own system to treat the obesity". (Emphasis added.) The present claims are directed to a method for the treatment of a patient having obesity comprising administering a compound capable of inducing OB-R expression and administering an OB-R agonist ligand, not "inducing expression of OB". Therefore, the present allegation regarding administration of an agent which induces expression of OB is irrelevant since the claims recite "OB-R" not "OB".

Furthermore, the Applicant respectfully submits that any allegation that the cited reference motivates one skilled in the art to use the claimed combination of agents would be the result of hindsight and speculation. It is required that there is a teaching in the cited reference that provides the motivation. The cited reference does not teach the elements of the claim or the combination thereof. The Examiner cannot use that which only the inventor taught against its teacher. See, e.g., *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 UPSQ 303, 313 (Fed. Cir. 1983). Accordingly, a *prima facie* case of obviousness has not been established by the Examiner and the rejection should be withdrawn.

Referring to page 7, lines 1-5 of the Office Action, the Examiner alleges that Grunfeld et al. discloses that endotoxins and cytokines increase expression of leptin/OB in response to infection. The present claims, however, do not require a response to infection or an increase in expression of leptin/OB. The Examiner alleges that the fact that the claimed invention recites different elements compared to the teachings Grunfeld et al., does not appear to influence the grounds of rejection. The differences between the claimed invention and the prior art; however, are one of four factual inquiries used to determine obviousness as a matter of law. See, e.g., *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). The Examiner may not discount the differences between the claimed invention and the prior art in making a determination of obviousness.

The Examiner alleges that the measured difference in weight loss between the present invention (16%) and the art (10%) is allegedly not significant or an unexpectedly greater amount of weight loss. The Applicants respectfully submit that the cited prior art reference does not disclose the claimed combination of administering a compound that is capable of inducing OB-R expression and administering an OB-R agonist ligand. The differences between the prior art and the claimed invention are part of the factual inquiry necessary to determine obviousness. The Examiner may not discount these differences.

Regarding the amount of weight loss, the specification discloses that the combination of administering an inducer of OB-R expression (e.g., LPS) and administering OB protein results in a significant reduction in body weight within twenty-four hours compared to the LPS alone (see, for instance, Example 4, Figure 15, and the brief description for Figure 15). Referring to Figure 15, LPS (10 micrograms LPS/gram body weight) was administered to each of two groups of mice. In addition to LPS, one group received vehicle (labeled "Control" in Figure 15) and the other group received OB protein (labeled "mOB" in

Figure 15). A significant difference in percent body weight between the two groups of mice is disclosed in Figure 15. Accordingly, not only does the prior art not teach or suggest the claimed combination, but the claimed combination yields unexpectedly superior results.

The Applicant respectfully requests that the Examiner withdraw the present rejection.

CONCLUSION

Claims 1-3, 6-7, 18, 20-24, and 26-31 are currently pending. Claims 1-3 and 6-7 are rejected under 35 U.S.C. § 112, First Paragraph, for allegedly not being enabled. The Applicants respectfully traverse the present rejection for the reasons on record, and as detailed above, and request that the Examiner place the present claims in condition for allowance.

Claims 18, 20-24, and 27 are rejected under 35 U.S.C. § 112, First Paragraph, for allegedly not being enabled. The Applicants respectfully traverse the present rejection for the reasons on record, and as detailed above, and request that the Examiner place the present claims in condition for allowance.

Claims 18, 20-24, 26, and 28-31 are rejected under 35 U.S.C. § 103(a) as allegedly not being patentable over Grunfeld et al (J. Clin. Invest. 97(9):2152-2157, 1996). The Applicants respectfully traverse the present rejection for the reasons on record, and as detailed above, and request that the Examiner place the present claims in condition for allowance.

The Applicant respectfully submits that all pending claims are in condition for allowance and requests that the Examiner allow all pending claims.

The Applicants have responded to all issues raised by the Examiner The Examiner is requested to contact the representative for

the Applicants, to discuss any questions or for clarification. No new matter is added by way of the present Response. If there are any further fees associated with this response, the Director is authorized to charge our Deposit Account No. 19-0962.

Respectfully submitted,

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Date

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